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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/422,528	10/21/1999	WOON-LAM Susan LEUNG	P1190R1	5652

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

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06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/422,528	LEUNG ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/21/1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 04/05/2007 has been entered.

2. Claims 1-13 and 15-25 are under consideration in this Office Action.

3. The rejections of claims 1-13 and 15-25 under 35 U.S.C. 103(a) stated in the previous Office Actions have been withdrawn in view of significant amendments to the claims in the amendment filed 04/15/2007. New rejections and grounds of rejection are presented in the instant Office Action.

Claim Rejections - 35 U.S.C. § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-13 and 15-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hart et al. (BIO/TECHNOLOGY Vol 12, November 1994; PTO 1449 dated 03/06/2000) in view of the combined teachings of Wetzel et al. (EP 0155189; PTO1449 dated 03/06/2000) and Van Dien et al. (Appl Environ Microbiol. 1997 May;63(5):1689-95; PTO 892).

Hart et al. teach a process for large scale production of IGF-I from the periplasm of *E.coli* comprising culturing *E.coli* host cell having a plasmid comprising an inducible alkaline phosphatase promoter and nucleic acid encoding a human IGF-I linked to a *lamB* signal sequence for secretion into the periplasm to (see entire publication, especially pp. 1113-115).

Wetzel et al. teach a plasmid vector comprising an inducible promoter and nucleic acid encoding a T4 phage lysozyme (see entire publication, especially pp.3-7 and claims1-9).

Van Dien et al. teach genes involved in polyphosphate metabolism in Escherichia coli were cloned behind different inducible promoters on separate plasmids. The gene coding for polyphosphate kinase was placed behind the P_{tac} promoter and its expression induced by the addition of IPTG. The gene coding for polyphosphatase was placed behind the P_{BAD} promoter and its expression induced by the addition of arabinose (see entire publication, especially RESULTS and DISCUSSION and pp. 1689-1693).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the nucleic acid encoding a T4 phage lysozyme taught by Wetzel el al. behind the arabinose inducible P_{BAD} promoter and/or place the nucleic acid encoding a human IGF-I linked to a *lamB* signal sequence for secretion into the periplasm taught by Hart et al. behind the IPTG inducible P_{tac} promoter. It would have been obvious to one of ordinary skill in the art to further transform the *E.coli* host cells taught by Hart et al. with the modified plasmid vector of Wetzel et al. and/or the modified plasmid vector having the nucleic acid encoding a human IGF-I linked to a *lamB* signal sequence placed behind the IPTG inducible P_{tac} promoter. It would have been obvious to one of ordinary skill in the art at the time the invention was made to culture the modified *E.coli* host cells, induce expression of human IGF-I by addition of IPTG where the expressed IGF-I is secreted into the periplasm, induce expression of T4 phage lysozyme by addition of arabinose after 50% or more of the human IGF-I has accumulated, the modified *E.coli* host cells are mechanically disrupted to release the IGF-I from the periplasm, and the IGF-I is recovered in the presence of EDTA.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have synthesis of lysozyme that ruptures the polysaccharide membrane of the *E.coli* host cell after accumulation of human IGF-I in the periplasm which simplifies the purification of the human IGF-I. One of ordinary skill in the art at the time the invention was made would have been motivated to wait until 50% or more of the human IGF-I has accumulated before inducing with arabinose to express T4 phage lysozyme in order to obtain a greater yield of human IGF-I. Furthermore, it would have been obvious to one of ordinary skill in the art to construct a vector having the nucleic acid encoding the T4 lysozyme and nucleic acid encoding human IGF-I on the same vector for the purposes of having a only a single vector which simplifies transformation in the *E.coli* host cell.

The art of recombinant heterologous protein expression in bacterial host cells is well developed and widely used in biotechnology for obtaining a desired protein. Thus, one of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success in that any desired protein can be produced by the modified method described above.

The reference of Dennis et al. (WO 93/24633. Published 12/09/1993) cited in the IDS dated 06/19/2000 teaches a recombinant *E.coli* host cell comprising a plasmid containing a biosynthetic pathway coding for poly-β-hydroxybutyrate and a plasmid containing a lysozyme

gene, and a process for the production an recovery of poly-β-hydroxybutyrate by culturing said recombinant *E.coli* host cell (see entire reference). The reference shows that lysozyme was important in the purification and recovery process of the product from the bacterial cell (see Examples 1-8). Thus, one of ordinary skill in the art ordinary skill in the art at the time the invention was made would be motivated to eliminate or reduce proteoglycan and polysaccharide components of the *E.coli* bacterial cell wall such that the *E.coli* host cell taught by Hart et al. is modified as described above. Elimination or reduction of proteoglycan and polysaccharide components of the *E.coli* bacterial cell wall by action of the expressed lysozyme would enable a simpler purification of IGF-I or of any desired protein.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

6. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hart et al. in view of the combined teachings of Wetzel et al. and Van Dien et al. as applied to the claims above, and further in view of Balbas et al. (Gene. 1996 Jun 12;172(1):65-9; PTO 892 reference of record).

Balbas et al. teach the plasmid pBRINT which is an efficient vector for chromosomal integration of cloned DNA into the lacZ gene of *Escherichia coli*, method for integrating cloned DNA into the *E.coli* chromosome using said plasmid pBRINT, and that integration of cloned DNA into the chromosome of the host organism is advantageous with respect to stability or undesired copy number effects (see entire publication).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the modified method of Hart et al. such that the nucleic acid encoding the human IGF-I is cloned into the plasmid pBRINT taught by Balbas et al. which in turn is integrated into the *E.coli* chromosome. One of ordinary skill in the art at the time the invention was made would have been motivated to do this to obtain stability of the nucleic acid encoding the human IGF-I and avoidance of undesired plasmid copy number effects as taught by Balbas et al. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-13 and 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "under conditions whereby the heterologous polypeptide is secreted into the periplasm of the bacteria as an aggregate and the phage lysozyme accumulates in the cytoplasmic compartment" which renders the claim vague and indefinite. The specific conditions where the heterologous polypeptide is secreted into the periplasm and the phage lysozyme accumulates in the cytoplasm are not defined and described in the specification and varies from one practitioner to another in the art of recombinant protein production technology . Thus, since one cannot determine the metes and bounds of the phrase, the claim is indefinite. Claims 2-25 which depend from claim 25 are also rejected because they do not correct the defect of claim 1.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

TEKCHAND SAIDHA
PRIMARY EXAMINER